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Is papillary thyroid microcarcinoma an indolent tumor?

A retrospective study on 280 cases treated with radioiodine

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Abstract

The increasing detection of papillary thyroid microcarcinoma (PTMC) has created management dilemmas. To clarify the clinical significance of postsurgery stimulated thyroglobulin (ps-Tg) in PTMC who undergo thyroidectomy and radioactive iodine (RAI), we retrospectively reviewed the 358 PTMC patients who were treated with RAI and followed up in our hospital. Those with an excessive anti-Tg antibody, ultrasound-detected residual were excluded, thereby resulting in the inclusion of 280 cases. Their clinical and histopathological information and clinical outcomes were collected and summarized. Tumor stages were classified according to the tumor, node, metastasis (TNM) staging system and the consensus of the European Thyroid Association (ETA) risk stratification system, respectively. Kaplan–Meier curves were constructed to compare the disease-free survival (DFS) rates of different risk-staging systems. By the end of follow-up, none of the patients died of the disease or relapsed. The 8-year DFS rate was 76.9%. Kaplan–Meier curves showed different DFS rates in TNM stages I versus IV, III versus IV, very low risk versus high risk, low risk versus high risk, respectively ($P < 0.05$), while they were not significantly different in stage I versus stage III, very low risk versus low risk ($P > 0.05$). Finally, 40 (14.3%) cases got a persistent disease. Five variables (male sex, nonconcurrent benign pathology, initial tumor size >5 mm, lymph node metastasis, and ps-Tg ≥ 10 μg/L) were associated with disease persistence by univariate regression analysis. Ps-Tg ≥ 10 μg/L was the only independent prognostic variable that predicted disease persistence by multivariate regression analysis (odds ratio: 36.057, $P = 0.000$). Therefore, PTMC with a small size of ≤1 cm does not always act as an indolent tumor. In conclusion, ps-Tg ≥ 10 μg/L is associated with increased odds of disease persistence. ETA risk stratification is more effective in predicting disease persistence than the TNM classification system.

Abbreviations: ^{131}I-WBS = ^{131}I-whole body scan, BRAF = b-type raf kinase, CT = computed tomography, DFS = disease-free survival, DSS = disease-specific survival, ETA = European Thyroid Association, LNM = lymph node metastasis, MR = magnetic resonance, OR = odds ratio, OS = overall survival, PET = ^{18}F-fluorodeoxyglucose positron emission tomography, ps-Tg = postsurgery stimulated thyroglobulin, PTC = papillary thyroid carcinoma, PTMC = papillary thyroid microcarcinoma, RAI = radioactive iodine, TC = thyroid cancer, US = ultrasound.

Keywords: disease-free survival, papillary thyroid microcarcinoma, risk factors, thyroglobulin, tumor staging

1. Introduction

Thyroid cancer (TC), which derives from the follicular epithelium, is the most common endocrine cancer, accounting for almost 1% of all cancers.[1] Owing to improvements in physical examinations and diagnostic imaging and likely alterations in the environment, the incidence of papillary thyroid microcarcinoma (PTMC) has been increasing worldwide, contributing markedly to the prevalence of papillary thyroid carcinoma (PTC). PTMC is defined as a small tumor (≤1 cm along the largest diameter) belonging to the well differentiated PTCs, which are often characterized by low malignancy, slow growth, minimal invasiveness, and low mortality.[2] They are frequently found in normal glands or nodular goiters. Several autopsy studies have also revealed that up to 36% of PTMCs have low aggressiveness, suggesting that PTMC is a common disease, typically with a perfect prognosis.[3–5]

However, distant metastases and death (0.4%–1% annually) have recently been reported to result from PTMC progression, indicating that a more aggressive approach should be adopted in treating PTMCs.[6,7] Since 2000, different guidelines and expert consensuses have been available to clinicians in China. Although several studies of TC have been reported in recent years, few reports on early predictors of clinical outcomes for PTMC patients with a long-term follow-up are available. Clinicians often believe that excellent prognosis is the inevitable consequence of the inert, ancient nature of the disease, whereas others believe that there are more important issues to discuss.[2,8,9] Therefore, there is a compelling need to understand PTMC better and to improve its management.

Editor: Gaurav Malhotra.

Funding/support: This work was supported by the Key Projects of Clinical Disciplines, Ministry of Health-subordinated Hospital, People's Republic of China (grant no. 2007-353).

The authors have no conflicts of interest to disclose.

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Medicine (2016) 95:40(e5067)

Received: 6 April 2016 / Received in final form: 11 September 2016 / Accepted: 11 September 2016

http://dx.doi.org/10.1097/MD.0000000000005067

In this paper, the clinical and histopathological information of PTMC patients were retrospectively analyzed. The aims were to report their clinical outcomes and to indicate factors that are predictive of persistent disease. In addition, the relationship between cancer risk stratification and clinical outcome was studied.

2. Patients and methods

This retrospective study was approved by the institutional review board of Huazhong University of Science and Technology. Written informed consent was obtained from the patients so that their information stored in the hospital database could be used for research.

2.1. Patients

The subjects included in this study were from the Department of Nuclear Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. From January 1, 2003 to June 30, 2014, a total of 2084 PTC patients were treated with radioiodine in our department, including 358 PTMC cases.

Among the 358 PTMC patients, 31 cases were excluded for excessive concentrations of anti-Tg antibody (beyond the upper limit of the reference range of 0–115 IU/mL), which interferes with the accuracy of serum Tg detection. Another 47 cases were excluded for detection of residual thyroid tissues by neck ultrasound (US), which influences the synthesis and secretion of Tg before initial radioactive iodine (RAI) therapy, and postsurgery stimulated thyroglobulin (ps-Tg) was considered to be one of the most important influencing factors related to clinical outcomes. Finally, 280 cases were enrolled in the study.

2.2. Postoperative treatment during the study period

2.2.1. RAI therapy. The indications for RAI therapy for the PTC patients were based on treatment guidelines from the 1996 edition of the American Thyroid Association guidelines.[10] The principal indications for patients to undergo RAI therapy included one or more of the following conditions: pathologic diagnosis of differentiated TC, bilateral total/near-total thyroidectomy, distant metastases, cervical node involvement, locally invasive neck disease, multifocal primary lesions, and evidence of disease residue or existence.

Initial RAI therapy was performed at 1 to 9 months after thyroid surgery. Then, RAI therapies were administered every 6 to 9 months during the first 2 years and then once per year, until disease-free status was achieved. Thyroxin withdrawal for 3 to 4 weeks was essential to achieve stimulated thyrotropin (TSH) of $\geq$30 mIU/L before RAI therapy. The dosages of radioiodine were individualized and based on clinical experience. For initial RAI therapy, patients showing stimulated Tg $\geq$ 10 μg/L, more than 5 involved cervical nodes, invasive neck disease, or distant metastasis were (^{131}I-NaI, Atomic Hi-Tech Co., Ltd., Beijing, China) administered at 5.55 GBq ^{131}I; patients without these features were treated at 3.7 GBq. Further, for subsequent RAI therapies, high or higher dosages (such as 5.55 or 7.4 GBq) were administered for a constant but static elevation of stimulated Tg $\geq$ 10 μg/L in patients with persistent disease. After 5 to 7 days of radioiodine administration, ^{131}I-whole body scan (^{131}I-WBS, by High-energy universal collimator, Millennium VG, GE) was carried out to evaluate whole-body iodine uptake.

2.2.2. TSH suppression. Levothyroxine (LT4) was used for replacement and suppressive treatment, based on European Thyroid Association (ETA) recommendations.[11] TSH suppression therapy ($\leq$0.1 mIU/L) was mandatory in patients with evidence of disease persistence, including Tg detectable with/without other evidence of residual TC. In patients declared as being complete remission or cured, there was a small possibility of recurrence, and the LT4 dose was decreased to achieve slightly higher TSH levels (0.5–1.0 mIU/L). In fact, if poor response to RAI was indicated, ^{131}I treatment would no longer be considered to achieve disease-free status in order to avoid further treatment toxicity. Instead, TSH suppression therapy (<0.1 mIU/L) using levothyroxine would be given as the primary treatment.

2.2.3. Follow-up. Follow-up was performed at 1 to 2 months after initial RAI therapy. Both stimulated and nonstimulated serum Tg, anti-Tg antibody, TSH, Rx-^{131}I-WBS, and neck US were assessed during the follow-up period. Serum Tg, anti-Tg antibody, and TSH were routinely detected (by a Cobas e 411 electrochemical luminescence analyzer, Roche, Sandhofer Strasse 116, 68305 Mannheim, Germany) to evaluate roughly the existence of the disease. Functional sensitivity for Tg measurement was 0.1 μg/L. The assay was also reproducible (intra- and interassay coefficients of variation <0.02 and 0.03, respectively). Rx-^{131}I-WBS was routinely conducted to find any lesions that had taken up ^{131}I. Neck US was utilized to determine the existence of residual thyroid tissue or enlarged lymph nodes. If local/regional or distant recurrences were suspected by clinical examination, further imaging and biological/cytological examinations would be carried out. Computed tomography (CT), magnetic resonance (MR), and ^{18}F-fluorodeoxyglucose positron emission tomography (PET)/CT would be applied when necessary.

2.3. Data variables

2.3.1. Baseline characteristics. The clinical and pathologic records collected included sex, age, concurrent benign pathology (such as Hashimoto thyroiditis, nodular goiter, adenoma, and Graves disease), tumor multifocality, bilobar lesions, tumor size, lymph node dissection, lymph node metastasis (LNM), multidissemination intrathyroid, extension beyond the thyroid, radiation exposure history, family history, and ps-Tg value. These variables were selected because they are the most examined potential factors related to the prognosis of PTMC patients.

Tumor multifocality was defined as 2 or more papillary lesions detected intrathyroid. Multidissemination intrathyroid was defined as satellite foci detected within the thyroid. Extension beyond the thyroid was defined as the invasion or infiltration of the local muscle, nerve, trachea, and vessels. All of the above were evaluated based on the final pathological examinations.

2.3.2. Outcomes. The clinical outcomes of the PTMC patients at the last follow-up were classified as follows: overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), persistent disease and local, regional, and distant recurrence.

OS was defined as the period between diagnosis and death. DFS was defined as the period after successful treatment during which there was no evidence of TC. DFS status required all of the following [12]: no clinical evidence of tumor; (b) no imaging evidence of tumor: no ^{131}I uptake outside the thyroid bed posttreatment WBS, or for uptake outside the thyroid bed, no evidence of tumor on a recent diagnostic scan and neck US; and undetectable serum Tg levels during TSH suppression and Tg < 2 μg/L with TSH stimulation in the absence of interfering

antibodies. DSS was defined as the period between primary surgery and death from TC and was calculated using the date of the last follow-up in our department. Patients who had evidence of progressive structural disease at the last follow-up or who died during the follow-up were considered to have died of TC. Persistent disease was defined as a patient who fails to meet the DFS standard after comprehensive treatments. Persistent disease meets any of the following items: stimulated serum Tg > 2 μg/L or unstimulated Tg > 1 μg/L; clinical evidence or imaging evidence (by ^{131}I-WBS, US, MRI, CT, or PET/CT) of tumor; and biopsy or cytology evidence. Local recurrence and regional recurrence were defined as papillary lesion recurrence in the intrathyroid bed and within the regional lymph nodes, respectively. Distant recurrence was defined as any recurrence of lesions beyond the cervical neck and the upper mediastinum and was confirmed pathologically and/or by radiological examination.

2.3.3. Risk stratification. Two stratification systems, the tumor, node, metastasis (TNM) staging[13] and ETA consensus risk stratification[11] systems, were applied in this study. TNM stage was defined in the guidelines of the American Joint Committee on Cancer Staging Manual.[13] According to the ETA consensus risk stratification system, very low risk was defined as unifocal T1 (≤1 cm) N0M0 and no extension beyond the thyroid capsule after surgery; low risk was defined as T1 (>1 cm) N0M0 or T2N0M0 or multifocal T1N0M0; and high risk was defined as any T3 and T4 or any T, N1 or any M1.

2.4. Statistical analysis

Time-independent continuous variables were evaluated using Student *t* test. Comparisons between categorical variables were performed using the Chi-square test or Fisher exact test, as appropriate. Univariate analysis was used for statistical correlations between the factors and outcomes. The multivariate logistic regression model was used to identify those factors independently associated with DFS. It included all of the variables with $P < 0.1$ in univariate analysis. The results are presented as odds ratios (ORs) with *P* values and 95% confidence intervals. Kaplan–Meier curves were constructed to compare DFS among patients from the different risk-staging systems, and the statistically significant variables were compared by multivariate analysis. All of the tests were 2-sided, and statistical significance was set at $P < 0.05$. Statistical Package for the Social Sciences software (version 17.0, SPSS Inc., Chicago, IL) was utilized for the data analyses.

3. Results

3.1. General baseline characteristics

The cases of PTMC included in this study consisted of 226 (80.7%) women and 54 (19.3%) men, with a female-to-male ratio of 4.19:1. The median age at the time of diagnosis was 43.0 (20–69) years. There were 66 cases whose ps-Tg was ≥10 μg/L. After 6 months of ablation, 49 (74.2%) of them had nonstimulated serum Tg > 2 μg/L, and 17 (25.8%) had Tg < 1 μg/L. The ^{131}I-WBS and other imaging results in those patients whose ps-Tg was ≥10 μg/L indicated remnant thyroid tissue or local/regional metastasis. The patient characteristics are shown in Table 1.

Table 1

Characteristics of patients in this study at baseline.

Characteristics	n
Total cases	280
Male	54 (19.3%)
Age (y, range)	43.0, 20–69
Concurrent benign pathology	118 (42.2%)
Hashimoto thyroiditis	57 (20.4%)
Nodular goiter	60 (21.4%)
Adenoma	18 (6.4%)
Graves disease	1 (0.4%)
Number of lesions	486
Unifocal	146 (52.1%)
Multifocal	134 (47.9%)
Bilobar multifocal	94 (33.6%)
Diameter, mm	6.7 (0.3–10)
Lymph node dissection	233 (83.2%)
LNM	156 (55.7%)
Number of LNM	571
Level VI	343 (60.1%)
Levels I–V	228 (39.9%)
Multidissemination intrathyroid	6 (2.1%)
Extrathyroid extension	15 (5.4%)
Radiation exposure history	2 (0.7%)
Family history	8 (2.9%)
Ps-Tg, μg/L	
≥10	66 (23.6%)
2–10	90 (32.1%)
≤2	124 (44.3%)
Average	18.5
TNM stage (seventh edition, 2009)	
I	224 (80.0%)
III	37 (13.2%)
IVA	18 (6.4%)
IVC	1 (0.4%)
Risk categories (ETA, 2006)	
Very low risk	54 (19.3%)
Low risk	65 (23.2%)
High risk	161 (57.5%)
RAI times (average, range)	1.4, 1–5
Personal dosage, mCi (average, range)	158 (100–850)

ETA = European Thyroid Association, LNM = lymph node metastasis, ps-Tg = postsurgery stimulated thyroglobulin, RAI = radioactive iodine, TNM = tumor, node, metastasis.

3.2. OS, DFS, DSS, persistent disease, and recurrence

The median follow-up time was 43.0 months (range, 13–121 months). None of the patients died during the follow-up period, and the OS/DSS rates were 100% at 2, 4, and 8 years, respectively. The 2-, 4-, and 8-year DFS rates were 85.2%, 84.3%, and 76.9%, respectively. The persistent disease developed in 40 (14.3%) cases and distant metastasis in 1 (0.4%). All of the 40 patients diagnosed with the persistent disease had elevated Tg, and 11 (27.5%) of them have both clinical/imaging (^{131}I-WBS/US/MR) evidence and biopsy/cytology evidence of remnant disease. Twenty-five (62.5%) cases had positive imaging findings but did not get proved by biopsy/cytology examinations. Another 4 (10.0%) cases had only elevated Tg, while imaging/biopsy/cytology examinations were negative (taken as "chemical persistent disease"). The diagnosis was based on the latest measured stimulated Tg, and Tg value of the 4 "chemical persistent disease" was 7.74, 10.32, 10.28, and 6.57 μg/L, respectively. None of the PTMC cases had recurrent disease.

3.3. DFS based on the risk stratification system

The DFS rates were different according to the different risk-stratification methods. The 2-, 4-, and 8-year DFS rates were stratified based on TNM stages and ETA stratifications (Table 2).

Table 2

DFS rates at 2, 4, 8 years were different when grouped by different risk stratification systems.

Risk stratification	2-year DFS, %	4-year DFS, %	8-year DFS, %
TNM			
I	87.6 (184/210)	86.2 (81/94)	81.8 (9/11)
III	85.7 (30/35)	72.7 (8/11)	50.0 (1/2)
IVA/C	57.9 (11/19)	75.0 (3/4)	–
ETA			
Very low risk	98.0 (50/51)	95.8 (33/34)	100 (7/7)
Low risk	93.5 (58/62)	84.0 (21/25)	–
High risk	77.5 (117/151)	78.0 (34/50)	50.0 (3/6)

DFS = disease-free survival, ETA = European Thyroid Association, TNM = tumor, node, metastasis.

3.4. Analysis of factors related to disease persistence

Univariate and multivariate regression analyses (Table 3) were applied to determine the latent factors related to survival with persistent disease. Five variables (male sex, lack of concurrent benign pathology, initial tumor size >5 mm, LNM, and ps-Tg ≥ 10 μg/L) were significantly related to persistent disease by univariate regression analysis. Ps-Tg ≥ 10 μg/L (OR 36.057, $P = 0.000$) was the only independent prognostic variable by multivariate regression analysis.

3.4.1. Kaplan–Meier curves. Kaplan–Meier curves were constructed to compare the overall DFS rates of different risk-staging systems. In the TNM staging system (Fig. 1A), the difference in DFS rate was statistically significant in stages I versus IV ($P = 0.003$, log-rank test) and III versus IV ($P = 0.013$). In the ETA risk stratification system (Fig. 1B), DFS differed when compared to very low-risk versus high-risk group ($P = 0.006$), as well as low-risk versus high-risk group ($P = 0.003$). P was >0.05 when compared to DFS rates between stages I versus III and very low-risk versus low-risk groups, respectively.

Kaplan–Meier curves were further conducted to estimate the DFS of PTMC patients with ps-Tg levels ≥ or <10 μg/L among all stages, using TNM staging (Fig. 2A–C) and the ETA stratification system (Fig. 2D–F). The curves showed that patients who had ps-Tg < 10 μg/L had a greater DFS rate than those who had ps-Tg ≥ 10 μg/L (Fig. 2A, B, E, and F). The difference for patients with stage IV disease did not approach significance (Fig. 2C); however, given that the total population in stage IV was quite small (n = 19), having ps-Tg ≥ 10 μg/L was not found to be statistically significant. Among very low-risk patients (n = 54), there was only 1 patient with ps-Tg ≥ 10 μg/L, and for this reason it was impossible to draw any conclusions (Fig. 2D).

4. Discussion

PTMC has become a public health concern owing to its sharp rise in incidence in the recent decades. However, its clinical significance remains controversial. Current treatment guidelines hold different opinions about treatment strategies for this disease,[11,12,14] for PTMC frequently have excellent outcomes. Herein, as observed, our cohort of 280 cases treated with radioiodine have favorable clinical outcomes as a whole. Nevertheless, the persistent disease developed in 40 (14.3%) cases and distant metastasis in 1 (0.4%). Ps-Tg ≥ 10 μg/L (OR 36.057, $P = 0.000$) was the only independent factor predictive of disease persistence by multivariate regression analysis. In consequence, all of these findings demonstrate that a small tumor size of ≤1 cm was not equivalent to a low risk of disease persistence.

PTC is the most common type of TC. However, a recurrence rate of 8% to 23% after surgical treatment has been reported.[15,16] Moreover, a recent meta-analysis reviewed 3523 PTMC cases with a median follow-up of 70 months, and the recurrence rate was 6.1% of all PTMC cases, and the rate was even higher (7.9%) in nonincidental PTMC cases.[2] As a result of the use of RAI therapy and TSH suppression, none of the cases relapsed in our series during the follow-up period, which was less than reported.

Ps-Tg ≥ 10 μg/L was highlighted as the only independent factor predictive of persistent disease by multivariate analysis. As confirmed by neck US before initial RAI therapy, no residual thyroid tissue contributed to ps-Tg. Therefore, ps-Tg represents residual lesions in the PTMC patients. The stimulated Tg level is a predictive factor in PTMC, as well as in other nonmicro PTC cases.[17,18] As concluded by a recent meta-analysis of 3947 PTC

Table 3

Univariate and multivariate analysis of parameters related to persistent disease.

Variables	Univariate analysis *P*	Multivariate analysis		
		P	OR	95% CI
Gender (male)	0.021*	0.072	2.926	0.908–9.427
Age (≥45 y)	0.328			
Concurrent benign pathology	0.003*	0.259	0.506	0.155–1.651
Initial tumor size (>5 mm)	0.059	0.068	3.529	0.911–13.670
Multifoci	0.330			
Bilobar	0.427			
LN dissection	0.190			
LNM	0.006*	0.120	2.959	0.752–11.636
Multidissemination intrathyroid	0.866			
Extension extrathyroid	0.170			
Radiation exposure history	0.431			
Family history	0.113			
Ps-Tg ≥ 10 μg/L	0.000*	0.000*	36.057	12.233–106.279
TNM stages III and IV vs stage I	0.136			
ETA high risk vs (very) low risk	0.400			

CI = confidence interval, ETA = European Thyroid Association, LN = lymph node, LNM = lymph node metastasis, OR = odds ratio, ps-Tg = postsurgery stimulated thyroglobulin, TNM = tumor, node, metastasis.
* $P < 0.05$.

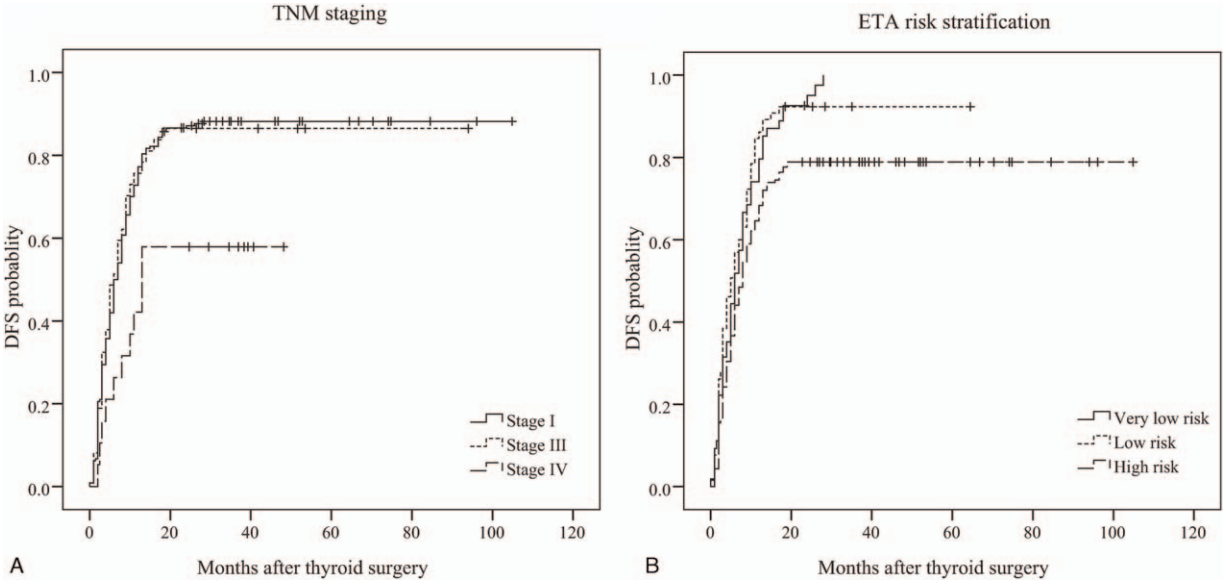

Figure 1. Kaplan–Meier disease-free survival (DFS) probability curves for the relationship between DFS and different tumor, node, metastasis (TNM) stages (A) or European Thyroid Association risk stratifications (B) were compared using the log-rank test (alpha = 0.05). DFS rate difference was statistically significant between stage I and IV, III and IV ($P < 0.005$) by TNM staging. DFS differs between very low-risk and high-risk groups, low-risk and high-risk groups ($P < 0.005$). P was >0.05 when compared to DFS rate between stage I and III, very low-risk and low-risk groups.

patients, preablation Tg < 10 μg/L was predictive of the absence of biochemical or structural evidence of disease at subsequent follow-ups.[19]

Male sex, lack of concurrent benign pathology, initial tumor size >5 mm, and cervical LNM were highlighted as risk factors for disease persistence, but not independently. A meta-analysis of 7408 nonmicro PTC reported that age was found to be a risk factor for disease recurrence in Western countries, whereas it was not identified as a risk factor in Asian countries.[20] The same study demonstrated that male sex, extrathyroid extension, LNM, tumor size >2 cm, distance metastasis, subtotal thyroidectomy, and ^{131}I not being administered were risk factors for TC recurrence.[20]

Hashimoto thyroiditis is one of the most frequently diagnosed inflammatory thyroid diseases and is the main cause of hypothyroidism.[21] The relationship between Hashimoto disease and PTC remains controversial.[22] As observed, the prevalence of Hashimoto thyroiditis is significantly higher in patients with PTC. Studies have revealed that the infiltration of lymphocytes to some extent represents a form of immune reaction that limits tumor growth and proliferation.[23] Meta-analyses have also suggested positive correlations of Hashimoto disease with DFS and OS.[24,25]

LNM is a strong predictor of persistent disease in PTC, as is well known.[26] Routine prophylactic central neck dissection is recommended only when preoperative enlarged lymph nodes suspicious of involvement are found by physical examination, an imaging study, or fine needle biopsy.[10,12,14] Some factors (age, male, tumor size, tumor foci, b-type raf kinase [BRAF] V600E mutation, human telomerase reverse transcriptase mutation, and tumor pathological staging) may associate with neck LNM.[27] Specifically, recent study[28] reported that age <45 years, multifocality, and extrathyroid extension were correlated with increased risk of central LNM, while the extrathyroid extension was associated with higher risk of lateral LNM. LNM rates were 29% of clinically suspected cases and 19% of unsuspected cases, respectively.[28] Consequently, there were a substantial number of PTMC patients who did not undergo lymph node dissection, which may be misclassified in the low/very low-risk group, considering the high incidence of LNM in our study (55.7%), as well as in previous studies.[28,29]

Good indicators to identify patients with latent nonindolent PTMC are urgently needed. Promising molecular markers, such as BRAF mutations, are in development.[30] A mutation in exon 15 of the BRAF gene has been noted to be a presumptive prognostic marker of the most prevalent form of PTC, which is a tumor type with high proclivity for recurrence or persistence,[31,32] whereas other studies have drawn the opposite conclusion that this mutation was not significantly correlated with aggressive clinicopathological features concerning the rates of nodal recurrence, distant metastases, or disease-specific death.[30] A recent meta-analysis involving 3437 PTMC patients presented an average prevalence of the BRAF mutation of 47.48%, and the mutation was associated with tumor multifocality, extrathyroidal extension, LNM, and advanced stage.[33] More studies are needed to understand better the clinical significance of BRAF mutations.

In the present study, a more radical treatment strategy was utilized in the current cohort, considering that LNM occurred in up to 55.7% of all cases, and the DFS rate at 8 years was only 76.9%. There was persistent disease after an average of 2.7 times of RAI therapies (range, 2–5 times) and 16.3 months of surgery (range, 12–47 months) at the time of data analysis. Despite several limitations inherent to its retrospective design (lack of strict designation and implementation plans), the results emphasized the crucial role of ps-Tg ≥ 10 μg/L in independently predicting disease persistence. The TNM staging system, based on this new perspective, is less effective in identifying patients with potentially high risk of disease persistence than the ETA stratification system. Thus, in conclusion, PTMC patients with ps-Tg ≥ 10 μg/L or higher risk stratification by ETA require more intensive treatments. This is based on our observation and needs further prospective studies to validate these data.

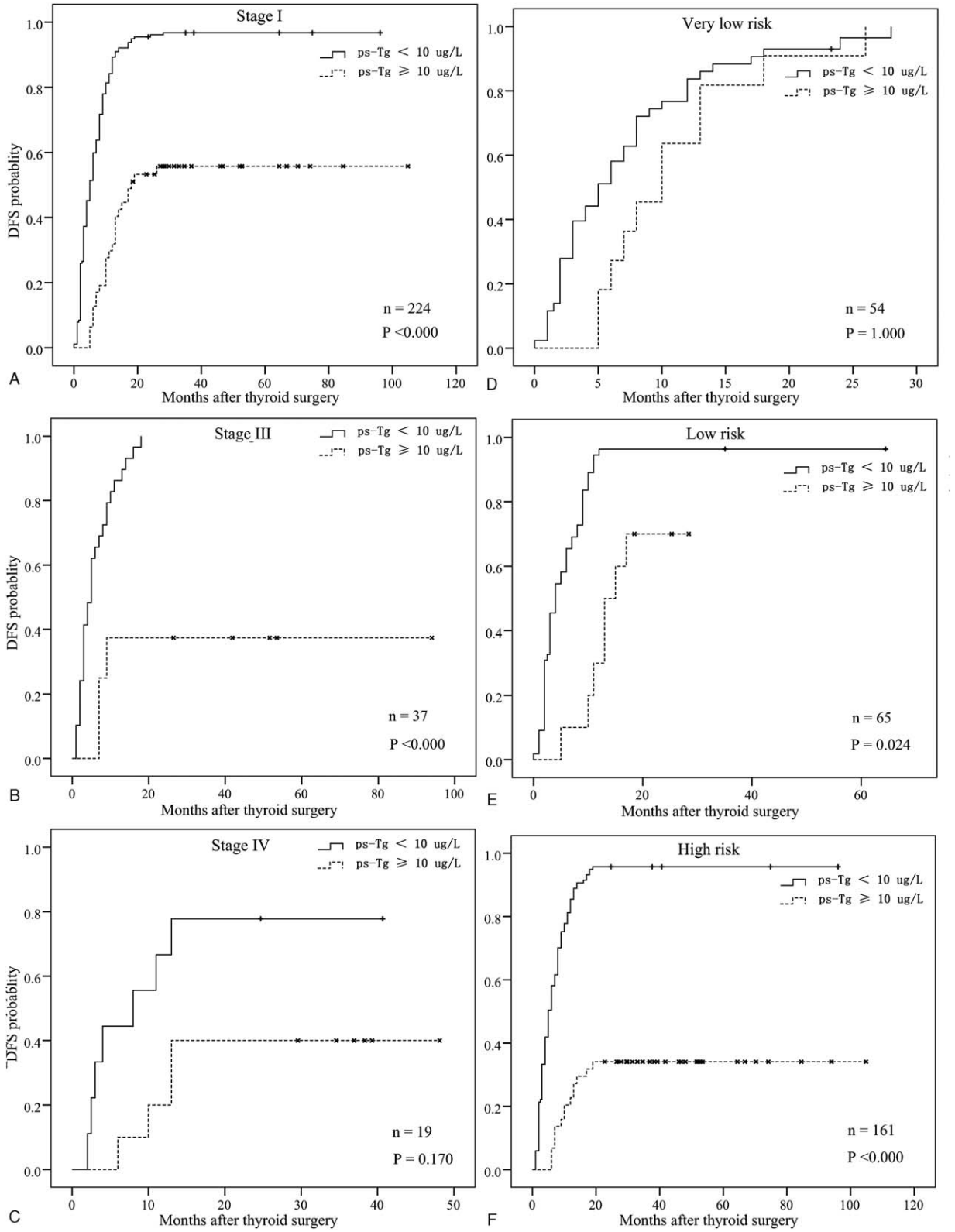

Figure 2. Kaplan–Meier disease-free survival (DFS) probability for different staging systems, tumor, node, metastasis (A–C) and European Thyroid Association (D–F), were restratified by postsurgery stimulated thyroglobulin (ps-Tg) level (10 μg/L) and compared using log-rank tests. Numbers of patients included (n) and corresponding *P* values were placed in each graph (lower right corner). (A), (B), (E), and (F) showed that patients who had ps-Tg < 10 μg/L had greater DFS rates than those who had ps-Tg ≥ 10 μg/L ($P < 0.05$). In (C), given that the total population in stage IV was quite small (n = 19), having ps-Tg ≥ 10 μg/L was not found to be statistically significant ($P > 0.05$). In (D), among very low-risk patients (n = 54), there was only 1 patient with ps-Tg ≥ 10 μg/L, and thus it was impossible to draw any reliable conclusions.

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